REMARKS

Applicant respectfully requests reconsideration. Claims 137-139, 141, 142, 144, 148, 149 and 164-175 were previously pending in this application. Claim 137 has been amended. Support for this amendment can be found in the specification at least on page 24 lines 29-32 through to page 25 lines 1-5. New claims 176 and 177 have been added. Support for new claim 176 can be found in the specification at least on page 2 lines 11-13. Support for new claim 177 can be found at least in the specification on page 2 lines 29-32 through to page 3 lines 1-3. As a result, claims 137-139, 141, 142, 144, 148, 149 and 164-177 are pending for examination with claims 137 and 177 being independent claims. No new matter has been added.

Claimed Invention

The claimed invention provides a unique method for detecting single polymers and distinguishing between wild type and mutant single polymers. The claimed method relates to the use of coincident binding of at least two probes onto a target mutant polymer. A first probe is specific for the mutant polymer (i.e., mutant-specific) while a second probe binds to both mutant and wild type polymers (i.e., polymer-specific). The probes are detectably and distinctly labeled. A mutant polymer will be bound by both probes, and therefore will have two detectable and distinct labels on it.

When both probes are bound to a mutant polymer, the labels (and their signals) are detected coincidently. There is a far lower probability of observing coincident signals if the polymer is wild type, even in the presence of unbound mutant-specific probes, because such probes will not exist in sufficient physical proximity to the wild type polymer. Similarly unbound mutant-specific and polymer-specific probes also will not exist in sufficient physical proximity to each other to generate coincident signals. The invention takes advantage of this coincident signaling to identify single mutant polymers.

Rejection under 35 U.S.C. §102

Claims 137-139, 141-142, 144, 148, 165-170 and 175 are rejected under 35 U.S.C. §102(b) as being anticipated by Chen et al. (Genome Research 1998) (hereinafter "Chen et al.").

Chen et al. teaches a method for detecting single nucleotide polymorphisms in DNA. The method is a two step enzymatic process that is performed in one reaction vessel. The first

step is amplification of a DNA sample using polymerase chain reaction (PCR). This is done in the presence of labeled probes which fail to bind to their target DNA due to the high annealing temperature. Once amplification is complete, the temperature is lowered, and the probes bind to their targets. The second step is a ligation reaction that ligates probes bound to a target DNA. The ligated probes (i.e., the ligation products) are then released from their target DNA and a plurality of ligated products are detected by gel electrophoresis. Allele-specific ligation products can be distinguished from each other based on migration distances in a gel. This process is illustrated in Figure 1 of the reference. The reference does not analyze target DNA when complexed with the labeled ligated probes, nor does it analyze single ligation products.

Claim 1 has been amended to include the limitation that the polymer being analyzed is not in vitro amplified. Support for this amendment can be found in the specification at least on page 24 lines 29-32 through to page 25 lines 1-5. The method of Chen et al. requires in vitro amplification via the PCR step. The method of claim 1 excludes in vitro amplification of the polymer being analyzed. At least for this reason, claim 1 and claims dependent thereon (including new claim 176) are not anticipated by Chen et al.

New claim 177 recites that complexes of polymers and first and second detectable labels are detected. Chen et al. does not analyze a target DNA/probe complex but rather analyzes the ligation products physically separated from the target DNA. (See for example Figure 2 of the reference.) Accordingly, claim 177 is not anticipated by Chen et al.

Reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §103

Chen et al. in view of Sokol et al.

Claims 172-173 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chen et al., as applied against claim 137 above and further in view of Sokol et al. (PNAS 1998).

As discussed above, Chen et al. does not anticipate claim 137 as currently amended, nor does it anticipate new claim 177.

A prima facie case of obviousness in view of Chen et al. and Sokol et al. has not been made. First, there is no motivation to combine the references. Chen et al. *requires* binding of *two* probes to a target DNA in order to form ligation products. Sokol et al. teaches binding of a *single* molecular beacon probe to target RNA. Second, there is no expectation of success since

the dual probe method of Chen et al. will not yield ligation products when combined with the single probe method of Sokol et al. Third, even if the combination could be made, it still does not yield an analysis of a non in vitro amplified polymer using two probes (claim 137) or detection of a complex of a polymer and two probes (claim 177).

Sokol et al. also reports a detection limit of about 10 target mRNA. For this additional reason, the combination of Chen et al. and Sokol et al. does not render obvious new claim 176 which recites detection of a single polymer.

Finally, Applicant finds no support for the Examiner's position that Sokol et al. teaches a mutant polymer fixed to a solid support. Sokol et al. introduces antisense probes for wild-type vav and β-actin RNA into K562 cells and then detects hybridization of the probes to their targets using confocal microscopy. The target RNA bound by the probes of Sokol et al. are *in vivo*, and they are not mutant.

Accordingly, the combination does not render obvious claim 137 as amended (and claims dependent thereon, including claims 172-173) and new claim 177.

Reconsideration and withdrawal of this rejection is respectfully requested.

Chen et al. in view of Rigler et al.

Claims 149, 170 and 174 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chen et al., as applied against claim 137 above and further in view of Rigler et al. (WO 03/076655).

As discussed above, Chen et al. does not anticipate claim 137 as currently amended, nor does it anticipate new claim 177.

Rigler is a German language PCT for which only an English translation of the one sentence abstract was provided. The abstract teaches that two or more probes are used to detect a nucleic acid. Figure 1 shows that the two probes may be molecular beacons. These teachings however were disclosed at least in the parent application of the instant application (i.e., serial number 10/448,264, filed on May 28, 2003, also being examined by the Examiner). Rigler et al. published on September 18, 2003, after the filing date of the parent application. Therefore, it is not prior art to teachings present in the parent application. These teachings include analysis of nucleic acids via coincident binding and detection of at least two detectable and distinct probes. For at least this reason, the combination of Chen et al. and Rigler et al. does not render obvious

claim 137 as amended (and claims dependent thereon including claims 149, 170 and 174) and new claim 177.

If the reference teaches instantly claimed limitations having a priority of only the filing date of the instant application, the Examiner is asked to identify such teachings and if possible provide an English language translation thereof.

Reconsideration and withdrawal of this rejection is respectfully requested.

Chen et al. in view of Stoughton et al.

As clarified in a brief telephone call with the Examiner on September 14, 2005, claim 139 is rejected under 35 U.S.C. §103(a) as being unpatentable over Chen et al., as applied against claim 137 above and further in view of Stoughton et al. (USPN 6,673,536).

As discussed above, Chen et al. does not anticipate claim 137 as currently amended, nor does it anticipate new claim 177.

A prima facie case of obviousness in view of Chen et al. and Stoughton et al. has not been made. First, there is no motivation to combine the teachings of the references. Stoughton et al. teaches a method for ranking polynucleotides according to their specificity for target probes based on their dissociation from the target probe with washes of increasing stringency. In this method, each polynucleotide is bound to a *single* probe. The method of Chen et al. *requires* the binding of *two* probes to a target DNA. Second, there can be no reasonable expectation of success of combining the dual probe method of Chen et al. with the single probe method of Stoughton et al. Third, even if the references could be combined, the combination does not yield an analysis of a non in vitro amplified polymer using two probes (claim 137) or detection of a complex of a polymer and two probes (claim 177). It therefore does not render obvious these claims or claims dependent thereon including claim 139.

The detection methods of Stoughton et al., including fluorescent readers for microarrays, require analysis of multiple copies of polynucleotides. For this additional reason, the combination of Chen et al. and Stoughton et al. does not render obvious new claim 176 which recites detection of a single polymer.

Reconsideration and withdrawal of this rejection is respectfully requested.

Chen et al. in view of Parker et al.

As clarified in a brief telephone call with the Examiner on September 14, 2005, claim 164 is rejected under 35 U.S.C. §103(a) as being unpatentable over Chen et al., as applied against claim 137 above and further in view of Parker et al. (USPN 5,565,323).

As discussed above, Chen et al. does not anticipate claim 137 as currently amended, nor does it anticipate new claim 177.

A prima facie case of obviousness in view of Chen et al. and Parker et al. has not been made. First, there is no motivation to combine the teachings of the references. Parker et al. teaches methods for detecting cytochrome oxidase mutations using normal and mutant specific probes, in some instances without prior amplification. However, Parker et al. does not teach simultaneous (or coincident) binding of the normal and mutant probes to a target DNA. Rather, the reference teaches that *duplicate* samples of target DNA are hybridized in parallel with one sample hybridized to the normal probe and the other sample hybridized to the mutant probe. Alternatively, the reference teaches that the same sample can be hybridized *sequentially* with both probes. (See column 16, lines 38-43.) The method of Chen et al. *requires* the *simultaneous* binding of *two* probes to a target DNA. Second, there can be no reasonable expectation of success of combining the dual probe method of Chen et al. with the single probe or sequential hybridization method of Parker et al. For at least these reasons, the combination does not render obvious claim 137 (claims dependent thereon including claim 139) and claim 177.

Reconsideration and withdrawal of this rejection is respectfully requested.

Claim Objection

Claim 171 is objected to as being dependent upon a rejected base claim but, according to the Examiner, would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

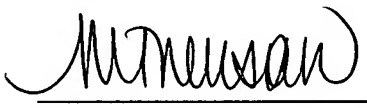
Applicant reserves the right to re-write claim 171 in independent form following consideration of this Amendment.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,



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